Clinical Commentary Review

Alternative Agents in Refractory Chronic Urticaria: Evidence and Considerations on Their Selection and Use

David A. Khan, MD *Dallas, Tex*

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Activity Objectives

1. To describe common adverse effects from alternative agents used in chronic urticaria.

2. To discuss the evidence in support of alternative agents in chronic urticaria.

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Patients with chronic urticaria (CU) who are refractory to antihistamines are frequently encountered by allergy specialists. Several alternative agents have been used to treat these patients; however, the evidence to support these agents is generally limited. This review focuses on some of the more commonly used alternative agents in refractory CU, including anti-inflammatory agents (montelukast, hydroxychloroquine, dapsone, sulfasalazine, methotrexate, colchicine), immunosuppressants (cyclosporine, tacrolimus, mycophenolate), and immunomodulatory agents (omalizumab, immune globulin). The evidence to support their use, dosing, potential toxicity, monitoring, and selection of these alternative agents is reviewed. Although numerous knowledge gaps exist for alternative agents in refractory CU, a rational, patient-based approach can be used with a goal of improving control and quality of life and minimizing adverse medication effects. © **2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;■:■-■)**

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Chronic urticaria (CU) is a common condition faced by allergists. Although antihistamines are the mainstay of therapy for CU, up to 40% of patients with CU may not achieve good control with antihistamine therapy.[1] Because patients with CU have significant morbidity and impaired quality of life, those patients refractory to antihistamines still require other therapies to control their disease. A number of drugs have been used to treat such patients with refractory CU. Some of these therapies possess immunosuppressant, anti-inflammatory, immunomodulatory, or other pharmacologic activities. These properties however do not apply to all of these therapeutic agents; therefore, these terms are not recommended to describe therapies as a whole for refractory CU. The term "alternative agents" has been proposed to describe any therapeutic agent other than antihistamines or corticosteroids used to treat patients with refractory CU.[2]

A number of alternative agents have been used to manage patients with refractory CU.[2,3] Unfortunately, the evidence to

Division of Allergy & Immunology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Tex

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Corresponding author: David A. Khan, MD, Division of Allergy & Immunology, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-8859. E-mail: dave.khan@utsouthwestern.edu.

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Abbreviations used
CU- Chronic urticaria
G6PD- Glucose-6-phosphate dehydrogenase
IVIG- Intravenous immunoglobulin

support the efficacy for most of these alternative agents is limited. Despite these limitations, clinicians can still use alternative agents to help manage patients with refractory CU to improve their quality of life and to limit toxicity from frequent or chronic use of systemic corticosteroids. This review discusses the evidence, practical considerations for choice, safety, and use of some of the more commonly used alternative agents for refractory CU. It is important to recognize that many alternative agents could be considered to possess multiple mechanisms of action (eg, both anti-inflammatory and immunosuppressant). For the purpose of this review, a somewhat arbitrary classification system has been developed in an attempt to organize these different therapies into one of the three following categories: (1) anti-inflammatory, (2) immunosuppressant, and (3) immunomodulatory.

ANTI-INFLAMMATORY ALTERNATIVE AGENTS

Several alternative agents that have predominately anti-inflammatory activities (and are not used in transplant rejection) have been reported to be efficacious in CU. In general, evidence for efficacy for these anti-inflammatory agents is fairly limited with few randomized controlled trials, typically with small numbers of patients. Toxicity for anti-inflammatory agents is generally low but varies by therapeutic agent, with some agents having the potential for rare but serious side effects.

Leukotriene receptor antagonists

Leukotrienes may have a role in the pathogenesis of CU as suggested by the fact that cysteinyl leukotrienes when injected into the skin cause a wheal and flare response.[4] Several case series and a few, mostly small, randomized controlled trials for leukotriene receptor antagonists exist for CU.[5-7] The results of these clinical trials show mixed results with some showing benefit[8-10] and others no benefit, either compared with placebo[11] or less efficacy then second-generation antihistamines.[6,12] Leukotriene receptor antagonists are generally viewed as safe medications; however, clinical experience with these agents has been largely disappointing in refractory CU. Because montelukast is generic, a short (few week) trial may be considered for patients with refractory CU.[13] In contrast to leukotriene receptor antagonists, 5-lipoxygenase inhibitors have not been studied in controlled trials with only a few case reports that suggest efficacy.[14,15]

Hydroxychloroquine

Hydroxychloroquine is an anti-inflammatory agent that disrupts T-cell receptor cross-linking–dependent calcium signaling and disrupts antigen processing; therefore, it has a potential benefit in CU. A single randomized, blinded, placebo-controlled study of 18 patients with CU treated with 12 weeks of 200 mg of hydroxychloroquine twice daily showed significant improvement of quality of life but only trends toward improvement in urticaria activity scores or concomitant medication reduction.[16] Because of dropouts, the study was underpowered to detect significant differences. A temporal lag of clinical improvement is well described in rheumatoid arthritis and a 12-week trial has been recommended in patients with CU.[16] Hydroxychloroquine is well tolerated with the most common adverse reactions related to gastrointestinal tract upset. The risk of retinopathy is low in the first 5 years of use, but after 5 years of use it increases to approximately 1%. Recent recommendations from the American Academy of Ophthalmology are a baseline ophthalmologic examination within the first year of starting hydroxychloroquine and then annual examinations after 5 years of therapy.[17] These recommendations also identify characteristics of high-risk patients for whom annual screening is recommended after drug initiation.

Dapsone

Dapsone is a sulfone antimicrobial with predominant anti-neutrophilic effects. It has been used in other neutrophil-rich cutaneous diseases. Nevertheless, it remains unproven whether patients with CU must have a neutrophil-rich infiltrate on biopsy to improve with dapsone. Evidence for dapsone in CU is limited. The largest report is a randomized, unblinded study of 38 patients with CU assigned to dapsone 50 mg daily plus desloratadine or of 27 control patients with CU treated with desloratadine alone for 3 months of treatment.[18] Both groups were followed an additional 3 months after all treatment was stopped. Although the dapsone-treated group had similar reductions in urticaria scores than the desloratadine monotherapy group, nine patients treated with dapsone had complete responses, whereas none of the control subjects did. In addition, five of nine responders remained urticaria free 3 months after discontinuing dapsone, suggesting that dapsone may induce remission of CU, as has been suggested in some other reports.[19,20] The preliminary results of a blinded, randomized controlled pilot study of dapsone 100 mg daily in 22 patients with CU treated for 6 weeks were recently reported.[21] Dapsone treatment showed significant improvement in itch, hive, and overall visual analog score at both 3 and 6 weeks of treatment.

Dapsone is usually well tolerated but has predictable side effects, including dose-related hemolysis. Asymptomatic methemoglobinemia is common; however, symptomatic methemoglobinemia (usually >15%-20%) is uncommon. Less common adverse effects include peripheral neuropathy, maculopapular exanthema, gastrointestinal tract complaints, hepatotoxicity, and rarely agranulocytosis or the syndrome of drug rash with eosinophilia and systemic symptoms. Before initiation of dapsone therapy, it is recommended to determine the level of glucose-6-phosphate dehydrogenase (G6PD) because dapsone should be avoided in G6PD-deficient patients because of the risk of severe hemolysis. Ongoing laboratory monitoring for anemia and hepatotoxicity is recommended.

Sulfasalazine

Sulfasalazine is an anti-inflammatory 5-aminosalicylic acid derivative. It has a number of anti-inflammatory effects with possible relevance to CU, including decreased leukotriene and prostaglandin production, inhibition of IgE-mediated mast cell degranulation, and inhibition of proliferation of B lymphocytes. Data with sulfasalazine in CU are limited to case reports and case series. The largest case series is a retrospective observational study of 19 patients with CU treated with sulfasalazine, starting at a dose of 500 mg daily and increasing by 500 mg weekly until satisfactory control was reached.[22] Fourteen patients showed

significant improvement, and two patients appeared to undergo remission with absence of urticaria after cessation of sulfasalazine. Therapeutic responses occurred within 1 month, and doses above 2 g/d had no additional benefit. Sulfasalazine has also been reported to be efficacious in a case report of two patients with delayed pressure urticaria/angioedema.[23] The most frequent side effects associated with sulfasalazine are gastrointestinal tract complaints such as nausea, vomiting, dyspepsia, and anorexia. Gastrointestinal tract symptoms typically occur early in therapy and are often dose related. Hematologic abnormalities, proteinuria, and hepatotoxicity are uncommon, and laboratory monitoring is recommended.

Methotrexate

Methotrexate is an anti-inflammatory agent (that also has immunosuppressant activity) with unclear mechanisms of action that include increasing adenosine levels, inducing apoptosis in activated $CD4^+$ T cells, and decreased neutrophil chemotaxis. Data with methotrexate in CU are limited to case reports and case series.[24,25] The largest case series with methotrexate is a retrospective study of 16 patients who required daily or frequent systemic steroids and failed antihistamines as well as a number of alternative agents.[25] Twelve of 16 patients responded to methotrexate with doses typically from 10 to 15 mg per week. There was a large range in time to response from 3 weeks to >6 months. Methotrexate showed some steroid-sparing effect, but only two patients were able to discontinue steroids. Methotrexate at low doses is frequently associated with toxicities, including gastrointestinal tract problems, stomatitis, headache, fatigue, and hematologic abnormalities. Serious complications such as hepatotoxicity, pulmonary toxicity, and myelosuppression are less common but still can occur with doses typically used in CU. Extensive and frequent laboratory monitoring is required with methotrexate.

Colchicine

Colchicine has a number of anti-inflammatory effects, including effects on neutrophils and adhesion molecules. Data with colchicine in CU are limited to a few case series, the largest with 36 patients (most with urticarial vasculitis)[26] and a negative randomized trial in delayed pressure urticarial.[27] The most common adverse effect with colchicine is diarrhea, but serious adverse effects are uncommon, and monitoring is minimal. The cost of colchicine has increased dramatically because a generic is no longer available.

IMMUNOSUPPRESSANT AGENTS

Immunosuppressant agents are medications typically used to prevent rejection in transplantation. These medications now have been used in a variety of other inflammatory conditions, including CU. Immunosuppressive medications have greater potential toxicity, but certain agents such as cyclosporine appear to be quite efficacious in refractory CU. Although the most robust data exist for cyclosporine, literature for all immunosuppressants is limited in scope and quality of evidence.

Cyclosporine

Cyclosporine binds to cyclophilin, and this complex inhibits calcineurin which has potent suppressive effects on T-lymphocyte function. Cyclosporine also has inhibitory effects on anti−IgE-induced histamine release from basophils and skin mast cells.

Although several observational and prospective studies of cyclosporine have been published in CU,[28-31] only two randomized double-blind placebo-controlled trials exist.[32,33] In the study by Grattan et al,[32] 8 of 19 subjects were considered responders (symptom scores < 25% of baseline) after 4 weeks of cyclosporine 5 mg/kg/d. Patients who were initially nonresponders or patients treated with placebo were offered open-label cyclosporine for an additional 8 weeks, and the overall response rate for all cyclosporine-treated patients was 65%. In addition, 25% of subjects were found to have complete remission with withdrawal of cyclosporine. Vena et al[33] compared two durations of cyclosporine therapy, 8 weeks compared with 16 weeks, and found improvement in urticaria severity in 62% of both groups with a 23% improvement in the placebo group. In this study cyclosporine was initially administered at 5 mg/kg/d and tapered down to 3 mg/kg/d over a period of 4 weeks. Both studies reported a high rate of side effects that ranged from 64% to 97% of subjects.

Low-dose cyclosporine studies have also been reported. Hollander at al[34] reported on a retrospective experience with 68 patients treated initially with 1 mg per kilogram of cyclosporine and increasing by 25 to 50 mg per day every 2 to 4 weeks until remission (≤1 day of hives per month) was achieved or a cyclosporine trough level of 100 to 200 ng/mL. Responders were tapered off cyclosporine after 6 months of therapy. They noted 78% underwent remission with average doses of 1.63 mg/kg/d. Adverse effects were lower with only 35% reported, and 6% required discontinuation due to adverse effects. With the use of this low-dose strategy, remission induction required 20 weeks on average, which is longer than higher-dose cyclosporine studies.

Other retrospective studies have found that both symptom improvement and adverse effects are dose related.[35] Another retrospective study of 20 patients with CU who continued on low-dose cyclosporine (1-2 mg/kg/d) for 5 to 10 years noted no significant long-term adverse effects.[36] Most patients were maintained with a cyclosporin A level of 50 ng/mL, which is in keeping with the concept that "therapeutic levels of cyclosporine" that are used for transplantation are not needed in patients with CU.

One of the main concerns with the use of cyclosporine is related to safety. Higher dose cyclosporine of >5 mg/kg/d has been associated with increased malignancy, infection, hypertension, and nephrotoxicity. Data on lower dose cyclosporine in patients with psoriasis or rheumatoid arthritis are more reassuring, with retrospective studies not finding any increase in malignancy rates after accounting for other risk factors.[37,38]

Nephrotoxicity is another concern with cyclosporine. Reports from cyclosporine in CU studies found increases in creatinine (>30%) in 0% to 9% of patients with resolution of renal dysfunction on discontinuing the cyclosporine.[29] Larger studies with cyclosporine use in psoriasis have found a slightly higher percentage of patients with increases in serum creatinine, with only a small percentage with persistent elevations in creatinine on discontinuation of cyclosporine.[39,40] Less-serious adverse effects are more common and include hirsutism, headache, paresthesias, nausea, abdominal pain, and hypertension. Given these adverse effects, blood pressure, renal function, and cyclosporine levels need to be monitored frequently with periodic monitoring for a variety of other laboratories because of the potential for

other metabolic derangements such as hyperglycemia or hyperlipidemia.

Tacrolimus

Tacrolimus is another calcineurin inhibitor that has a different binding protein (FK-506 binding protein) than cyclosporine. Similar to cyclosporine, tacrolimus has also been shown to inhibit anti−IgE-mediated mast cell and basophil granulation.

Only one small retrospective study exists for tacrolimus in CU. Nineteen patients with refractory CU were treated in a dose-tapering fashion, starting with 0.05 to 0.07 mg/kg/d down to 1 mg a day over 12 weeks.[41] Two patients had to discontinue tacrolimus because of severe abdominal pain, diarrhea, and headache. Twelve of the 17 remaining patients (70%) had improvement in symptoms within 5 to 10 days. Mild diarrhea was observed in 50% of responders and paresthesias were reported in 2 patients. Three of 12 responders remained in remission of urticaria 3 months after tacolimus was discontinued. Tacrolimus has similar serious adverse effects as cyclosporine; however, compared with cyclosporine, there is less risk of hirsutism and gingival hyperplasia.

Mycophenolate

Mycophenolate is another immunosuppressant agent used in transplantation as well as a growing number of autoimmune diseases. The active metabolite of mycophenolate is a competitive inhibitor of inosine-5′-monophosphate dehydrogenase and kills activated lymphocytes through the activation of a caspase-independent necrotic signal. An open-label study of nine patients with refractory CU were treated with 12 weeks of mycophenolate mofetil 1000 mg twice daily and showed improvement in urticarial scores and medication use, including systemic steroids.[42] In a retrospective series, 19 patients with CU, most refractory to other alternative therapies, were treated with mycophenolate mofetil in doses that ranged from 1 to 6 g/d divided into twice-daily doses.[43] Time to initial response ranged from 1 to 9 weeks with complete control of urticaria achieved in 60% of patients after a mean treatment of 14 weeks with a median dose of 4000 mg/d. Remission of urticaria was noted in six patients after discontinuation of mycophenolate with follow-up ranged from 2 to 16 weeks. The most common adverse effects in both of the studies were gastrointestinal tract symptoms, ranging from 20% to 53% of patients.

Mycophenolate has less serious adverse effects than the calcineurin inhibitors, particularly the absence of nephrotoxicity. Hematologic side effects, including leukopenia, are less common, usually mild, reversible, and dose related. Mycophenolate-treated patients are at increased risk of opportunistic infections, including shingles and cytomegalovirus. Importantly, mycophenolate is associated with miscarriage and congenital malformations when used in pregnancy; therefore, it should be avoided in women trying to conceive.

IMMUNOMODULATORY AGENTS

Immunomodulatory agents, often referred to as “biologic” therapies, have a number of mechanisms of activity that may include anti-inflammatory and immunosuppressant activity. The agents in these categories comprise antibody therapies, including monoclonal antibodies and cytokine or cytokine receptor-targeted therapies.

Omalizumab

Omalizumab is a monoclonal antibody directed against IgE that is approved for poorly controlled moderate-to-severe asthma. Omalizumab reduces free IgE and downregulates expression of the high-affinity IgE receptor on mast cells and basophils. The exact mechanism of how omalizumab works in CU is unclear, but it has been hypothesized that IgE autoantibodies may exist, as has already been shown for IgE antithyroperoxidase antibodies in a subset of patients with CU.[44]

Numerous case reports initially suggested the efficacy of omalizumab in CU. In addition to chronic idiopathic urticaria, reports of efficacy exist for other physical urticarias, including solar, cold, delayed pressure, dermographism, and cholinergic urticaria, as well as idiopathic angioedema.[45] More recently randomized controlled trials have been performed to document the efficacy of omalizumab.

A multicenter, randomized, double-blind placebo-controlled dose-ranging study of a single dose of omalizumab was performed in 90 patients with CU refractory to antihistamine therapy.[46] Statistically significant improvement over placebo was noted in both the 300-mg and 600-mg omalizumab groups but not the 75-mg group. Most of the clinical effect occurred within the first 2 weeks of therapy. Complete resolution of CU was noted in 36% of the 300-mg omalizumab group, 28.6% of the 600-mg omalizumab group compared with 4.4% in the 75-mg omalizumab group and 0% in the placebo group. Omalizumab was well tolerated in this study.

A second randomized multicenter trial studied 49 patients with persistent CU all of whom had IgE autoantibodies to thyroperoxidase.[44] Of 341 eligible patients 292 were excluded, including 160 who had IgE autoantibodies to thyroperoxidase that were deemed “too low.” Omalizumab was dosed according to asthma dosing, and the primary end point was improvement in urticaria activity score after 24 weeks of treatment. Compared with placebo, the omalizumab-treated group showed a statistically significant greater mean reduction in weekly urticaria activity score. Complete protection from wheal development was observed in 70% of patients in the omalizumab group compared with only one patient (4.5%) in the placebo group.

The most recent randomized multicenter double-blind study evaluated omalizumab in 323 patients with CU who were symptomatic despite conventional doses of antihistamines.[47] This is the largest randomized trial of any alternative therapy in CU. Patients were treated with omalizumab every 4 weeks at doses of 75 mg, 150 mg, or 300 mg or placebo, followed by a 16-week observation period. The primary outcome was change in weekly itch score. Both the 150-mg and 300-mg omalizumab groups showed statistically significant improvement in both itch and hive scores compared with the placebo group. Complete resolution of hives and itching was noted in 44% of the 300-mg omalizumab group, 22% of the 150-mg omalizumab group, 16% of the 75-mg omalizumab group, and 5% of placebo-treated patients. The median time to a minimally important difference response was 1 week for the 300-mg omalizumab group and 2 weeks for the 150-mg group. After discontinuation of omalizumab, symptom scores worsened and were similar to placebo, suggesting that there was no long-term effect in remission of CU. Adverse effects were similar to those reported with asthma, and most of the serious adverse events occurred in the group receiving the highest dose of omalizumab.

Compared with other alternative agents, omalizumab appears to have the most robust data and is generally safe. Omalizumab is costly and is typically cost-prohibitive if not covered by insurance. In contrast to asthma, there are no pharmacoeconomic data on its use in CU. Because of its expense, requirement for administration in an office setting, and difficulty with accessibility (because of insurers' general reluctance to approve its use in CU), its precise role relative to other alternative agents remains unclear.

Immune globulin

Intravenous immunoglobulin (IVIG) has a variety of immunomodulatory activities that could potentially have an important role in CU, including modulation of adhesion, complement function, cytokine levels, and autoantibodies. The earliest report of IVIG and CU was an open-label trial of 10 patients who had failed other therapies, including alternative agents.[48] Patients were treated with an immunomodulatory dose of IVIG at 0.4 g/kg/d for 5 consecutive days. Nine of 10 patients reported benefit with three patients experiencing prolonged remission. Other case reports have suggested benefit of IVIG with other dose regimens[49,50]; however, failures have also been reported. The lowest dose regimen reported to be effective was an open-label study of 29 patients with CU treated with 0.15 g/kg/d every 4 weeks.[49] In contrast to the higher dose studies, consistent improvement in CU was achieved after a mean of 4.5 months.

IVIG is relatively safe with predictable infusion-related adverse reactions and rarely more serious reactions such as anaphylactoid reactions, aseptic meningitis, or renal failure. However, the overall data on efficacy are limited. Although typically generally well tolerated, its high expense and requirement for prolonged infusions limits its role in the management of CU.

Other immunomodulatory agents

Data with other immunomodulatory agents are largely limited to case reports or small case series. TNF inhibitors such as etanercept, infliximab, and adalimumab have been reported to be effective in a single patient with delayed pressure urticaria[51] and in three patients with CU who were refractory to other alternative agents.[52] B cell−targeted therapies that used rituximab have also been reported to be successful in some case reports of refractory CU[53,54] and idiopathic angioedema,[55] but negative reports exist as well.[56] Anti−IL-1 therapies are established therapies in autoinflammatory syndromes, but only a few case reports suggest efficacy of anakinra in idiopathic cold urticaria[57] and delayed pressure urticaria.[58]

SELECTING AN ALTERNATIVE AGENT

Choosing a specific alternative agent for a patient with refractory CU can be accomplished with a rational approach. Before initiation of an alternative agent, it is important to establish that the patient is indeed refractory to antihistamine therapy with appropriate dose advancements. In patients who do not respond to higher doses of second-generation antihistamines, use of potent H1-antagonists (eg, hydroxyzine, doxepin) in higher doses (eg, 75-150 mg/d) can often lead to control of CU. Comorbid factors also should be considered in determining alternative agents. For example, in patients with poorly controlled hypertension, cyclosporine may exacerbate their hypertension. Baseline laboratory testing is typically required to determine whether any agents are contraindicated (eg, dapsone and hydroxychloroquine with G6PD deficiency). Evidence of CU-related autoantibodies is not helpful in predicting responses to alternative agents. The cost of alternative agents varies considerably; thus, affordability is another important treatment consideration. The frequency of treatment-related visits (eg, omalizumab injections) should also be a consideration for certain patients. Rapidity of response as well as potential for remission can also be factors that influence the decision of a given alternative agent. Finally, and perhaps most important, is the potential risk of a given alternative agent. This potential risk needs to be weighed against the patient's quality of life and any adverse effects from their current therapy, such as systemic steroids for their CU. It is essential to have a discussion with the patient to weigh the risks and benefits of various alternative agents and to engage the patient in the decision-making process for his or her refractory CU.

Taken as a group, anti-inflammatory agents are generally less toxic than immunosuppressants and many immunomodulatory agents and have a lower risk of serious long-term adverse effects. Nevertheless, these agents have less-proven efficacy and appear to have a slower onset of action. One approach is to use these agents in patients with refractory CU who do not require chronic systemic steroid use. Immunosuppressant agents, when used in higher doses, have a more rapid response, potential for remission, and greater efficacy. These factors need to be weighed against higher adverse effects. Low doses of immunosuppressive agents are clearly less toxic but also have a slower onset of action, and their efficacy in refractory CU has not been well established. For patients who require frequent or daily corticosteroids, or patients already experiencing adverse steroid-induced effects, immunosuppressive agents may be an attractive option. Among the immunomodulatory agents, omalizumab clearly appears to be the most efficacious, well studied, and safe agent. Limitations for its use in CU are primarily cost and hence accessibility, as well as potential for remission. If available, omalizumab is certainly an attractive option for refractory CU, especially in those patients who have failed other alternative agents. Some suggested dosing regimens as well as monitoring for various alternative agents are outlined in Table I. Table E1 (in the Online Repository available at www.jaci-inpractice.org) lists various alternative agents that have been reported to have complete responses (absence of urticaria and symptoms).

DURATION OF TREATMENT AND CONCOMITANT MEDICATIONS

Once an effective alternative agent has been determined, other medications for CU can often be tapered or discontinued. Some patients may still derive some benefit from additional antihistamines, whereas other patients who are completely antihistamine refractory can have all of their antihistamines discontinued. The optimal duration of therapy for alternative agents in CU is unknown. One approach, especially for patients with long-standing CU, is to treat patients who have achieved minimal or no urticaria with an alternative agent for an additional 3 months before tapering the dosage. A tapering strategy of approximately 25% of the dose on a monthly basis can be used for many of the anti-inflammatories and immunosuppressive agents. In the case of omalizumab, reducing the frequency of injections from every 4 weeks to every 6 weeks or longer can also be an effective tapering strategy. Most patients with refractory CU can be

TABLE I. Selected alternative agents for refractory chronic urticaria

Alternative agent	Typical dose	Onset of improvement	Estimated effectiveness	Evidence	Risk (pregnancy category)*	Laboratory monitoring	Cost	Induction of remission†
Anti-inflammatory agents								
Montelukast	10 mg daily	2-4 wk	Low	Multiple RCT (mixed results)	Minimal (B)	None	$$	Unknown
Hydroxychloroquine	200 mg twice daily	Up to 12 wk	Moderate	1 RCT	Low (C)	Baseline: G6PD, LFT, BUN/Cr	$	Unknown
Dapsone	100 mg daily with reduction of dose as tolerated	1-6 wk	Moderate	1 RCT	Low-moderate (C)	Baseline: G6PD, CBC, LFT Monthly: CBC, LFT × 6 mo then periodically	$	Possible
Sulfasalazine	500 mg twice daily, increasing to 1 g twice daily	<4 wk	Moderate	Case series	Low (C)	Baseline: CBC, LFT, BUN/Cr Monthly: CBC, LFT, BUN/Cr × 3 mo then every 3 mo	$	Possible
Methotrexate	10-15 mg weekly	1-6 mo	Moderate	Case series	Moderate-high (X)	Baseline: CBC, LFT, BUN/Cr, CXR Every 2-4 wk: CBC, LFT, BUN/Cr	$	Unknown
Colchicine	0.6 mg twice daily	Unclear	Low-moderate	Case series	Low (C)	Baseline: LFT, BUN/Cr	$$$	Unknown
Immunosuppressant agents								
Cyclosporine								
Low dose	1-2 mg/kg/d	<4 wk	Moderate-high	Case series	Low-moderate (C)	Baseline: CBC, LFT, BUN/Cr, K, lipids	$$$	Possible
Higher dose	3-5 mg/kg/d	1-7 d	High	2 RCTs	Moderate-high (C)	Every 2-4 wk: BUN/Cr, K, CSA Periodic: lipids, glucose		
Tacrolimus	1 mg twice daily, increasing to 2-3 mg twice/d if needed	1-2 wk	High	Case series	Moderate-high (C)	Same as cyclosporine except check tacrolimus levels	$$$	Possible
Mycophenolate	1000 mg twice daily, increasing to 4-6 g/d if needed	1-9 wk	Moderate	Case series	Moderate-high (D)	Baseline: CBC, LFT, BUN/Cr First month: weekly CBC, then every 2 wk for 2-3 mo then monthly	$$$	Possible
Immunomodulatory agents								
Omalizumab	150-300 mg every 4 wk	1-2 wk	High	3 RCTs	Low-moderate (B)	None	$$$$	Unknown
Immune globulin	150-400 mg/kg every 4 wk or daily × 5 d	High dose: 2 wk Low dose: 4-5 mo	Moderate	Case series	Low-moderate (C)	Baseline: BUN/Cr, CBC Periodic monitoring of BUN/Cr, CBC	$$$$	Possible

BUN, Blood urea nitrogen; *CBC*, complete blood count; *Cr*, creatinine; *CSA*, cyclosporine; *CXR*, chest x-ray; *K*, potassium; *LFT*, liver function test; *RCT*, randomized controlled trial.

**Category B*, Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women; *Category C*, animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; *Category D*, positive evidence of human fetal risk is based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; *Category X*, studies in animals or humans have demonstrated fetal abnormalities and/or positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

†Induction of remission that was based on reports of resolution of urticaria after therapy has been discontinued.

treated with an alternative agent for several months and then be able to taper or discontinue the therapy. However, some patients with CU may require prolonged use of an alternative agent for years.

KNOWLEDGE GAPS

Numerous gaps in our knowledge about alternative agents in CU exist. Large, controlled, well-designed randomized trials have not been conducted for most of the alternative agents. Furthermore, comparative trials among various alternative agents or even high-dose antihistamine therapy do not exist. Long-term safety for alternative agents in patients with CU is also unclear and may be different than in populations in whom these agents are typically used. The true potential for inducing remission of CU is also unknown for most all of these agents. Despite these limitations, a rational, patient-based approach can still be used that is based on evidence, potential for adverse effects, costs, and patient preferences.

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TABLE E1. Alternative agents and reports of complete response in CU

Medication	No. of subjects with CU*	Treatment duration	Type of study	Study duration/follow-up	Percentage of complete responders	Reference
Montelukast	9	3 mo	Obs	3 mo	56	Criado et al[5]
	10	2 wk	Obs	2 wk	0	Godse[6]
Dapsone	22	6 wk	DBPC	15 wk	14	Cooke et al[21]
Sulfasalazine	19	2-24 mo	Obs	9 mo (mean)	37	McGirt et al[22]
Methotrexate	10	NR	Obs	NR	10	Perez et al[25]
	8	2-12 mo	Obs	2-15 mo	87	Sagi et al[24]
Colchicine	7	0.5-9 mo	Obs	NR	43	Pho et al[26]
Cyclosporine	23	5 mo	Obs	3-6 mo	87	Boubouka et al[30]
	40	20 wk	Obs	20 wk	40	Di Gioacchino et al[31]
	27	4 wk	Obs	4 wk	4	Serhat Inaloz et al[28]
	68	10 mo (mean)	Obs	60 wk (mean)	78†	Hollander et al[34]
Tacrolimus	19	12 wk	Obs	3-6 mo	47‡	Kessel et al[41]
Mycophenolate	19	21 wk (mean)	Obs	NR	53	Zimmerman et al[43]
Omalizumab	27	24 wk	DBPC	24 wk	70	Maurer et al[44]
	243	12 wk	DBPC	28 wk	16-44	Maurer et al[47]
Immune globulin	10	5 d	Obs	8-24 wk	60	O'Donnell et al[48]
	6	2 d to 12 mo	Obs	11-24 mo	83	Mitzel-Kaoukhov et al[50]
	29	6-51 mo	Obs	12 mo	66	Pereira et al[49]

DBPC, Double-blind, placebo controlled; *NR*, not reported; *Obs*, observational.
Complete responders were defined as 100% response (no urticaria/symptoms).
*Patients with urticarial vasculitis were not included.
†Experienced $\leq$1 day of urticarial per month.
‡Scores of 0 to 1 were reported.